PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 4928PTWO/AG/LA	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/EP2004/050371	International filing date *(day/month/year)* 26.03.2004	Priority date *(day/month/year)* 26.03.2004
International Patent Classification (IPC) or national classification and IPC INV. A61K9/72 A61K9/16 A61K38/28		
Applicant UNIVERSITA' DEGLI STUDI DI PARMA		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 1 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☒ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
25.01.2006	14.07.2006
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized officer Epskamp, S Telephone No. +31 70 340-2857

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/050371

Box No. I Basis of the report

1. With regard to the **language**, this report is based on

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3(a) and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4(a))
   - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages	
1-12	as originally filed
Claims, Numbers	
1-6	filed with telefax on 24.02.2006
Drawings, Sheets	
1/1	as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☒ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☒ the claims, Nos. 1
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/050371

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-6
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-6
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-6
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item I

Basis of the report

The amendments filed with the letter dated 24/2/2006 introduce subject-matter which extends beyond the content of the application as filed, contrary to Article 34(2)(b) PCT. The amendment concerned is the following: New claim 1 has been based on (*inter alia*) original claims 1 and 4. However, claim 4 related to a powder with a respirable fraction (aerodynamic diameter < 5 µm) of **more than** (not including) 80%. No basis could be found for the feature that exactly 80% of the particles have an aerodynamic diameter lower than 5 µm, as it is presently claimed in claim 1.

For the purpose of the remainder of this Report it will be assumed that indeed present claim 1 contains the feature "more than 80% of them exhibiting an aerodynamic diameter lower than 5 µm" instead of the contested feature.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: Forbes RT et al. (1998) J. Pharm. Sci. 87: 1316-1321
D2: WO 02/053190 A
D3: Todo H et al. (2001) Int. J. Pharm. 220: 101-110
D4: WO 01/93837 A
D5: WO 99/55362 A
D6: Quaglia F et al. (2003) J. Control. Release 86: 267-278
D7: EP 0 505 966 A

Novelty

1 - Claims 1-6 are considered novel (Article 33(2) PCT).

2 - Document D1 discloses particles for inhalation, obtained by spray drying of insulin in HCl/glycine buffer pH 2.4, optionally in the presence of mannitol or lactose (abstract; page 1317, right-hand column, par. 2).

3 - D2 discloses particles for inhalation obtained by spray drying a solution of insulin, DPPG and sodium citrate in ethanol/water, pH 4.0 (formulation number 5 of the examples). Again, given the disclosed aerodynamic and geometric size and density (see table 2), and the similar preparation process, claims 1-7 and 10-15 lack novelty over D2.

4 - In document D3 insulin dry powders are prepared by spray drying a solution comprising insulin, mannitol and citric acid (abstract; § 2.2.2 and Table 2 (formulations MIC0.1 and MIC0.2); §§ 3.2 and 3.4, and Table 2 and Figures 3b and c; § 4).
5 - Document D4 discloses spray drying a solution of insulin and sodium citrate, pH 2.0 (page 18, line 25 - page 20, line 25; example 1).
6 - Document D5 discloses spray -dried IGF-1 powders for inhalation, preferably obtained by spray drying from an acetic acid solution (page 4, line 22 - page 5, line 16; page 11, line 15 - page 12, line 5; examples: formulations B and C; page 26, lines 7-14).
7 - Documents D6 (abstract; § 2.2) and D7 (example 1; claims) disclose spray drying solutions of insulin (D6) or busurelin acetate (D7) and PLGA in acetic acid, resulting in particles which are larger than presently claimed.

Inventive Step

1 - Claims 1-6 also fulfill the requirements with regard to inventive step (Article 33(3) PCT).
2 - D1 is seen as the closest state of the art. Present claim 1 differs from D1, in that it defines particles obtained by spray drying from an unbuffered acetic acid solution.
The problem to be solved could be seen as to provide insulin particles with a higher stability.
Claim 1 is inventive, as neither D1 nor any of the other documents suggests to use an unbuffered acetic acid solution instead of a buffered acidic solution to obtain more stable insulin particles.

Industrial Applicability

Claims 1-6 fulfill the requirements of Article 33(3) PCT.

NEW SET OF CLAIMS

1. Microparticles stable at room temperature of insulin, optionally in association with excipients selected from the group consisting of saccharides, polysaccharides, aminoacids, phospolipids and polyalcohol ,

   said microparticles:

   - being obtained by spray drying an aqueous solution of insulin having an acid pH under the isoelectric point (5.4) of insulin and a concentration of insulin in amounts of from 5 to 100 mg/ml,
   - showing a d90 volume diameter lower than 9 μm,
   - 80% of them exhibiting an aerodynamic diameter lower than 5 μm,
   - containing less than 10% by weight of salts,

   characterised in that said aqueous solution of insulin to be spray dried is prepared in an unbuffered aqueous solution of acetic acid.
2. Microparticles according to anyone of claims 1 or 2 having a tapped density lower than 0.2 g/cm^3.
3. Microparticles according to claim 2, wherein said excipient is mannitol.
4. Microparticles according to anyone of claim 1-3 containing insulin in amorphous form.
5. Pharmaceutical compositions suitable to be inhaled containing the microparticles according to anyone of claims 1-4
6. The pharmaceutical compositions according to claim 5 consisting of the microparticles according to anyone of claims 1-4.